PennState

HRP-592 - Protocol for Human Subject Research with Use of Test Article(s)

Protocol Title:

Effects of Random Nicotine Delivery on Smoking Cessation

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1.0 Objectives

1.1 Study Objectives

The objective of this study is to determine whether treatment with random nicotine delivery via nicotine film both before and after the quit date will facilitate cessation relative to treatment with steady state delivery or placebo. We hypothesize that smoking cessation will be greater in subjects assigned to a random nicotine delivery regimen (as compared to those assigned to a steady state or placebo regimen). The nicotine film product is not part of the standard of care and is not available in non-investigational settings in the United States.

1.2 Primary Study Endpoints

The primary endpoints for the study include the percent reduction in the number of cigarettes smoked and the accompanying percent reduction in exhaled carbon monoxide (CO) levels.

1.3 Secondary Study Endpoints

The secondary endpoints include subjective ratings of the films and side effects.

2.0 Background

2.1 Scientific Background and Gaps

According to the CDC, cigarette smoking is associated with profound morbidity and mortality. In the United States alone, cigarette smoking is responsible for about 480,000 deaths per year[1] and costs the nation more than $300 billion annually.[2] About 15% of all adults smoke in the United States and by 12th grade, 42% of students report having smoked. Starting, however, is one problem and stopping is another. Cigarette smoking is a disease of chronic relapse. Indeed, once having started, smokers will make as many as 20 quit attempts before they are successful[3] and abstinence rates can be as low as 7%, even following NRT with the patch, gum, or nasal spray.[4] As with other addictions, cue-induced craving contributes to relapse following a quit attempt.[5]

From a global perspective, it would seem that there are three options for the treatment of cigarette smoking: no support (unaided cessation), behavioral support of one manner or another, and/or pharmacological intervention. With nearly 70% of smokers reporting that they would like to quit, yet most failing, we must assume that will, alone, is not sufficient. Certainly, the ability to quit any addiction can be bolstered by behavioral and/or pharmacological support. Contingency management is a behavioral intervention where abstinence is reinforced with tangible incentives such as money. However, individuals addicted to smoking may be insensitive to the very reward upon which their behavior is contingent.[6,7] NRT is a long-standing and widely used smoking cessation tool. Yet, as discussed, NRT too is only modestly effective. We propose that the limited effectiveness of NRT is due, at least in part, to a failure to prevent cue-induced craving and relapse. In support, NRT treatment does not attenuate stimulus-elicited drug seeking. Here we propose a novel alternative to the steady-state delivery of nicotine (i.e., to the standard patch) for the treatment of smoking cessation. Specifically, we propose to use an oral film to treat smokers wishing to quit with random, rather than steady-state, delivery of nicotine prior to and following the quit date.

2.2 Previous Data

Support for our random delivery hypothesis is provided by both preclinical and clinical data suggesting that yoked (i.e., uncontrollable/unpredictable) delivery of drug impairs the development of cue-drug associations, retards or disrupts responding for drug or alcohol, and can even render the drug aversive. In rats, yoked delivery of ethanol retarded later acquisition of ethanol self-administration[8] and, in our hands, a history of yoked delivery of cocaine[9] disrupted the willingness to work for the drug on a progressive ratio schedule of reinforcement. Although fixed ratio (FR) responding appears normal in rats with a history of yoked delivery of cocaine, the averaged data occlude the fact that rats yoked to high

drug-takers actually took only about 4 infusions/hour on the FR schedule. To be effective, however, yoked delivery of drug needs not only delay acquisition in drug inexperienced rats, but must effectively rescue subjects with a strong drug habit. In accordance, Twining and Mueller (in preparation) found that yoked delivery of cocaine rescued cocaine-experienced rats by reducing drug seeking during extinction and by reducing drug-taking during subsequent FR testing. In humans, Donny et al[10] reported that yoked delivery of cocaine led to an increase in mean systolic and diastolic blood pressure in response to the drug because of a lack of cue-supported tolerance. Scheduled availability of ethanol led to a marked decrease in intake of ethanol in a controlled setting.[11] Finally, a meta-analysis showed that pre-cessation treatment with a standard (i.e., steady state) nicotine patch doubled the odds of quitting smoking relative to subjects that received only post-cessation treatment with the nicotine patch.[12-14] Rose and Behm, too, found abstinence enhanced by pre-cessation treatment with the nicotine patch.[15] Foulds reported that use of the nicotine patch while smoking led to a 14% reduction in expired carbon monoxide (CO), reduced satisfaction from smoking, and fewer and weaker reported urges to smoke.[16] These marked effects are thought to be due, at least in part, to separation of blood nicotine levels from the act of smoking.[15] Dissociation of smoking behavior and cues from nicotine is expected to be even greater with random nicotine delivery.

2.3 Study Rationale

There is, as yet, no 'random patch'. Random delivery via a subcutaneously placed chip or pump is conceivable, but would be invasive and expensive. Here we propose to test the merits of our hypothesis simply by using a trans-mucosal nicotine orally dissolving film that has been tested and is safe for use in humans.[17,18] In a pharmacokinetics study, we found that plasma nicotine levels achieved by the nicotine film are similar to those resulting from consumption of equivalent doses of other oral NRT products.[19] The films were well-tolerated in this study and produced mild side effects that were similar in nature to those of currently available NRT.[19] The film is easy to use and tastes pleasant to humans. No water is required, as the film simply adheres to the roof of the mouth until dissolved (less than 5 minutes). Indeed, unlike nicotine gum, there are no complicated instructions regarding how and when to chew. The film can be used to deliver any dose of nicotine desired over time and placebo films are readily available. Finally, if the hypothesis proves correct, this novel treatment should be fairly inexpensive and available over the counter. As such, it will be both accessible and affordable, even for low-income smokers.

If this 'random film' were to work as predicted, cigarette cues would be dissociated from the act of smoking, smokers maintained on the random film would be more likely to achieve cessation. This would be a remarkable advance for the treatment of smoking and would inform the treatment of other addictions as well.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

1. Aged 18-55
2. Smoke ≥10 cigarettes/day for at least the past 12 months
3. Exhaled CO measurement ≥6 ppm at baseline visit
4. Interested in completely ceasing cigarette consumption and using a nicotine film product as directed
5. Willing to attend regular visits over a 6-week period (not planning to move, not planning extended vacation, no planned surgeries)
6. Able to read and write in English
7. Able to understand and consent to study procedures

3.2 Exclusion Criteria

1. Unstable or significant medical conditions and conditions such as elevated blood pressure (systolic >159 mmHg or diastolic >99mmHg at baseline), COPD, and those conditions that are likely to affect participant safety such as kidney or liver disease
2. Individuals with sodium-restricted diet, heart disease, recent heart attack, irregular heartbeat, stomach ulcers, or diabetes as well as those taking prescription medications for depression or asthma as indicated under "Warnings" section on FDA approved NRT Drug Facts Label
3. More than weekly use in the past 3 months of illegal drugs or prescription drugs that are not being used for medically prescribed purposes
4. Use of non-cigarette nicotine delivery product in the prior 7 days (including cigars, pipes, chew, snus, hookah, electronic cigarette and marijuana mixed with tobacco)
5. Use of an FDA approved cessation medication in the past 7 days (any NRT, Chantix, Wellbutrin)
6. Women who are pregnant (verified by urine pregnancy test at baseline visit), trying to become pregnant, or nursing
7. Uncontrolled mental illness or substance abuse or inpatient treatment for these conditions in the past 6 months
8. Any previous adverse reaction to NRT
9. Any other condition, serious illness, or situation that would, in the investigator's opinion, make it unlikely that the participant could comply with the study protocol
10. Other member of household currently participating in the study

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

The PI reserves the right to remove a participant from the study for any reason, based on their discretion in order to protect the safety of a participant.

3.3.1.1 Withdrawal prior to randomization

Participants who meet any criteria below at Visit 2 will be considered for withdrawal prior to randomization:

- Not smoking ≥10 cigarettes/day for at least 5 out of the past 7 days
- Use of a non-cigarette nicotine delivery product in the past 7 days
- Reporting a quit attempt in the past 30 days

3.3.1.2 General withdrawal criteria

Participants may be discontinued by the PI at any point during the study for any of the following reasons:

- **Missing their study visit window**: If a participant misses their study visit window, the participant will be considered for withdrawal from the study.
- **New pregnancy**: Participants who report a new pregnancy at any point during the study will be withdrawn.
- **Cardiovascular disease (CVD) event requiring inpatient hospitalization**: CVD typically includes MI (heart attack), PTCA (angioplasty/stenting), bypass surgery, stroke, peripheral vascular disease (arterial blockages in arms or legs leading to procedure or surgery). Less common CVD problems would be new cardiac arrhythmias (e.g., new atrial fibrillation) or new vavlular disease (e.g., mitral or aortic regurgitation).
- **DVT/PE (deep vein thrombosis/pulmonary embolism, i.e., blood clots in the venous system) requiring inpatient hospitalization**.
- **Adverse events related to nicotine film use**: Adverse events, including symptoms of nicotine overdose (nausea, vomiting, dizziness, weakness, or

rapid heartbeat) or allergic reactions to the nicotine film, will be monitored at every study visit.

- **Worsening substance abuse** in which the participant is behaving inappropriately at visits or demonstrates an inability to continue with the study.
- **Any inpatient hospitalization or debilitation** in which participation in the study could be detrimental to the recovery process. This will be self-reported by the participant and will be reviewed by the site PI and medical professional to determine whether continued participation in the study is appropriate (this could include recovery from a major surgery, worsening of psychiatric symptoms, etc.).
- **Any situation where participant is not able to use their study product for a period of more than 2 weeks** (e.g., incarceration or other similar situation) unless they report non-study product use by choice.
- **Participant choice**: Participants may choose to remove themselves from the study by informing the research team in writing at any point during the study. If they choose to remove themselves from the study, they will not receive any further contact from the study center.
- **Participant behavior**: If a participant is behaving in an inappropriate or threatening manner, admits to lying about eligibility criteria, is participating in other smoking research studies that could affect the primary outcome measures, appears/admits to giving away/selling study products, consistently loses study products, etc., then the PI can withdraw him/her from the study at the PI's discretion.

3.3.2 Follow-up for withdrawn subjects

If participants are withdrawn from the study for any of the reasons noted above prior to randomization, they will be replaced until a total of 45 participants have been randomized to the study. Reasons for withdrawal will be ascertained from subjects who voluntarily withdraw from the study (See End of Trial Form).

4.0 Recruitment Methods

4.1 Identification of subjects

All recruitment for this study will be routed through IRB STUDY00002213 which will also serve as the initial recruitment point of contact.

4.2 Recruitment process

Interested volunteers calling the study center number will first complete the eligibility script and questions for IRB STUDY00002213. If a participant's responses match this study's specified inclusion criteria they will be forwarded to research staff for further screening.

4.3 Recruitment materials

See IRB STUDY00002213.

4.4 Eligibility/screening of subjects

1. **Screener 1 (Phone):** We will consider the screening process and eligibility questions in IRB STUDY00002213 as Screener 1. This process includes a brief phone screening to determine basic eligibility for any of our study center protocols. Then, participants will complete the screening for this study in two additional steps.

2. **Screener 2 (Phone):** A full script and screening questions specific to this study are in the "Consent Forms and Recruitment Materials" section of the IRB application.

3. **Screener 3 (In person, Visit 1):** After a participant has met basic eligibility criteria over the phone, they will be scheduled to come into the study center where they will be consented to the study and further screened for eligibility. See section 7.2 for further details.

5.0 Consent Process and Documentation

5.1 Consent Process

5.1.1 Obtaining Informed Consent

5.1.1.1 Timing and Location of Consent

When participants attend their first in-person visit, they will have the study explained to them in detail, have the opportunity to ask questions, and then will be asked to sign the consent form. Participants will be given a signed copy of the form. This will take place in a private clinic room at the Penn State Clinical Research Center.

5.1.1.2 Coercion or Undue Influence during Consent

Once potential study volunteers are identified, they will be given information about the study and offered the opportunity to participate. The researchers obtaining consent will be instructed to clearly indicate that the participant's enrolling in the trial is purely voluntary and the researchers will not offer comments about whether they believe the participant should enroll in the study or not. Compensation provided to the participant is modest.

5.1.2 Waiver or alteration of the informed consent requirement

N/A

5.2 Consent Documentation

5.2.1 Written Documentation of Consent

An IRB-approved consent form will be used to document written consent. The participant will be given a copy of the signed consent. The participant's signed consent form will be uploaded into the participant's REDCap record.

5.2.2 Waiver of Documentation of Consent (Implied consent, Verbal consent, etc.)

Participants who are interested in the study will be asked to consent to allow the researcher to pre-screen them for the study over the phone by asking all screening questions of all participants (eligible or ineligible). Participants will be asked if this information can be retained so that the study team will know reasons that participants are not eligible for the study.

In addition, participants who are not eligible for the study, or those who begin the phone screener but are not interested in completing it after learning more about the study, will be asked if they would be interested in being contacted for future studies being conducted by our research team. They will be informed that by providing their name and phone number, they will be consenting to allow the study team to contact them in the future.

5.3 Consent – Other Considerations

5.3.1 Non-English Speaking Subjects
N/A

5.3.2 Cognitively Impaired Adults
N/A

5.3.2.2 Capability of Providing Consent
N/A

5.3.2.3 Adults Unable To Consent
N/A

5.3.2.4 Assent of Adults Unable to Consent
N/A

5.3.3 Subjects who are not yet adults (infants, children, teenagers)
N/A

5.3.3.2 Parental Permission
N/A

5.3.3.3 Assent of subjects who are not yet adults
N/A

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☒ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☐ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☒ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure

Information is included in the "Confidentiality, Privacy and Data Management" section of this protocol.

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

All study data will be retained indefinitely. Paper records will be kept in a safe area in Dr. Grigson's locked research office.

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

The phone screener (Screener 2) will be used to check eligibility criteria (date of birth), and when participants are screened, their contact information will be used to follow-up about scheduling and for appointment reminders. This requires that we have complete contact (name, phone number) information.

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

In order to screen the participants prior to inviting them into the study center, the investigators are conducting a phone screening to determine if the participants are likely to be eligible for the study.

6.3 Waiver or alteration of authorization statements of agreement

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted uses and disclosures according to federal regulations.

The research team will collect only information essential to the study and in accord with the 'Minimum Necessary' standard (information reasonably necessary to accomplish the objectives of the research) per federal regulations.

Access to the information will be limited, to the greatest extent possible, within the research team. All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

7.0 Study Design and Procedures

7.1 Study Design

This is a randomized, double-blind, placebo-controlled, parallel-group study that will occur in three phases over 7 weeks.

Time & Events Table								
	Baseline	**Pre-Cessation**		**Cessation**				
Study Week Number	-1	0	1	2	3	4	5	6
Study Visit Number	**1**	**2**	**Ph #1**	**3**	**Ph #2**	**4**	**Ph #3**	**5**
Study Day Number	-7	0	7	14	21	28	35	42
MEASURES								
Screener 3	X							
Concomitant medications	X	X	X	X	X	X	X	X
Medical history	X							

NIDA Quick Screen	X							
Cigarette details	X							
Adverse events		X	X	X	X	X	X	X
Daily cigarette/film diary collection		X	X	X	X	X	X	X
Demographics	X							
Tobacco Use History	X							
Environmental Tobacco Smoke Questionnaire		X		X		X		X
Cigarette Evaluation Scale		X	X	X	X	X	X	X
Nicotine dependence		X		X		X		X
Minnesota Withdrawal Scale		X		X		X		X
Questionnaire Smoking Urge		X		X		X		X
Perceived Stress		X		X		X		X
Confidence to quit		X		X		X		X
Study product side effects			X	X	X	X	X	X
Study product evaluation			X	X	X	X	X	X
Likelihood of Use Scale				X		X		X
Dose Awareness								X
BIOMEASURES								
Height		X						
Weight		X		X		X		X
Waist/Hip ratio		X						X
Exhaled CO	X	X		X		X		X
Blood pressure & pulse	X	X		X		X		X
Pregnancy test	X			X		X		

7.2 Study Procedures

7.2.1 Baseline Phase – Visit 1 (Consent Visit, Day -7)

At the first study visit, the following procedures will be conducted:

7.2.1.1 Prior to informed consent procedures, participants will complete the same screening questions completed over the phone previously (via Screener 2) to confirm eligibility (Screener 3). If participant meets eligibility criteria assessed via Screener 3, they will continue with Visit 1 and be asked to provide informed consent.

7.2.1.2 Pregnancy exclusion will be confirmed through a urine test that will be self-administered by the participants when they come to this visit. Participants with confirmed pregnancy will be withdrawn from the study and the End of Trial form will be completed.

7.2.1.3 Medical history will be documented to ensure that the participant does not have any conditions that may make them ineligible for the study.

7.2.1.4 Concomitant medication history will be recorded to ensure that the participant is not taking any medications that may make them ineligible for the study.

7.2.1.5 Details of participants' usual brand cigarettes, including brand name and other characteristics, such as flavor, will be recorded.

7.2.1.6 Exhaled CO ≥6 ppm will be confirmed. Participants with a CO reading lower than 6 ppm will be withdrawn from the study and the End of Trial form will be completed.

7.2.1.7 The NIDA Quick Screen will be administered and participants indicating the use of prescription drugs for non-medical use, illicit drugs, and/or marijuana daily, almost daily, or weekly over the past 3 months will be withdrawn from the study and the End of Trial form will be completed.

7.2.1.8 Blood pressure and pulse will be measured. Participants with a blood pressure of systolic >159 mmHg or diastolic >99 mmHg will be withdrawn from the study and the End of Trial form will be completed.

7.2.1.9 Participants who meet all eligibility criteria will complete the measures indicated on the Time & Events Table for the baseline visit. Measures will be completed electronically on a participant computer via REDCap. Participants will be given a laptop with access only to the internet, and an individualized REDCap survey will be opened so they can complete direct data entry.

7.2.1.10 Participants will be instructed to continue smoking their usual brand of cigarettes for the next week, to avoid using any other tobacco products, and to maintain a daily diary of cigarette use on which they will record the number of cigarettes they smoke each day.

7.2.1.11 Participants will be compensated for completing the study visit and procedures.

7.2.2 Pre-Cessation Phase – Visit 2 [1 week after Visit 1] (Day 0 -1/+3 days)

7.2.2.1 Adverse events will be documented.

7.2.2.2 The cigarette daily diary will be reviewed and recorded by the researcher to confirm that the participant completed their diary, that ≥10 cigarettes were smoked on at least 5 out of the last 7 days, and that no quit attempts have been reported. If any of these criteria have not been fulfilled, the participant will be excluded from randomization, and the End of Trial Form will be completed.

7.2.2.3 Use of other tobacco products in the past 7 days will be assessed. If the participant has used any other tobacco product in the past 7 days, they will be excluded from randomization, and the End of Trial Form will be completed.

7.2.2.4 Concomitant medications will be assessed to confirm participants have not initiated nicotine replacement therapy or cessation medication use since Visit 1. If they have initiated either of these medication categories, they will be excluded from randomization, and the End of Trial Form will be completed.

7.2.2.5 Participants who meet all eligibility criteria for randomization will complete the measures and study procedures indicated on the Time & Events Table for the visit.

7.2.2.6 Following randomization, subjects will receive their assigned study products. Research staff will explain how to use the nicotine films and provide participants with administration and dosing instructions. Participants will receive a 14-day plus 3-day supply of the assigned film regimen (68 films total). The films will be packaged and numbered so they are taken in a specific, sequential order throughout each day. Participants will be instructed to take one film every 3-4 hours each day for a total of 4 films per day.

7.2.2.7 Participants will be asked to return all used (opened/empty) and unused (unopened) study product pouches at their next study visit.

7.2.2.8 Participants will be instructed to continue smoking their usual brand of cigarettes ad libitum over the next two weeks and to avoid using any other tobacco products.

7.2.2.9 Participants will be instructed to maintain a daily diary of both their cigarette use and nicotine film use. This diary will require that they record the number of cigarettes they smoke each day and the time of day each film was taken.

7.2.2.10 Participants will be compensated for completing the study visit and procedures.

7.2.3 Pre-Cessation Phase – Phone Call #1 (Day 7 ± 3 days)

During this phone contact, daily cigarette/film diary information will be collected, adverse events and changes to concomitant medications will be documented, and participants will be asked to verbally answer the measures indicated in the Time and Events Table during the phone call. Participants' answers will be entered directly into REDCap by the researcher at the time of the call.

7.2.4 Cessation Phase – Visit 3 (Day 14 ± 3 days)

At this in-person visit, the following procedures will be conducted:

7.2.4.1 Adverse events will be documented, and any concomitant medication changes will be recorded.

7.2.4.2 The daily cigarette/film diary will be collected and recorded by the researcher. Use of other tobacco products in the past 7 days will also be assessed.

7.2.4.3 Participants will complete the measures and study procedures indicated in the Time & Events Table.

7.2.4.4 All nicotine pouches from the previous weeks (unopened, opened, or empty) will be collected by the researcher.

7.2.4.5 Participants will be provided with a new supply of their assigned nicotine films (14-day plus 3-day supply [68 films total]) to use over the next two weeks until their next study visit.

7.2.4.6 Participants will be asked to return all used (opened/empty) and unused (unopened) study product pouches at their next study visit.

7.2.4.7 Participants will be instructed to cease all cigarette use and to only use their assigned nicotine films beginning the next morning.

7.2.4.8 Participants will be provided with the document from the Centers for Disease Control and Prevention titled, "A Report of the Surgeon General: How Tobacco Smoke Causes Disease." Participants will also be given a document with tips to prepare and succeed in a quit attempt.

7.2.4.9 Participants will be instructed to continue to maintain a daily diary of their nicotine film use. This diary will require that they record the time of day each film was taken. Participants will be instructed to only record cigarettes smoked on their diary in the event that they experience a slip.

7.2.4.10 Participants will be compensated for completing the study visit and procedures.

7.2.5 Cessation Phase – Phone Call #2 (Day 21 ± 3 days)

During this phone contact, daily nicotine cigarette/film diary information will be collected, adverse events or changes to concomitant medications will be documented, and participants will be asked to verbally answer the measures indicated in the Time and Events Table during the phone call. Participants' answers will be entered directly into REDCap by the researcher at the time of the call.

7.2.6 Cessation Phase – Visit 4 (Day 28 ± 3 days)

At this in-person visit, the following procedures will be conducted:

7.2.6.1 Adverse events will be documented, and any concomitant medication changes will be recorded.

7.2.6.2 The daily cigarette/film diary will be collected and recorded by the researcher. Use of other tobacco products in the past 7 days will also be assessed.

7.2.6.3 Participants will complete the measures and study procedures indicated in the Time & Events Table.

7.2.6.4 All nicotine pouches from the previous weeks (unopened, opened, or empty) will be collected by the researcher

7.2.6.5 Participants will be provided with a new supply of their assigned nicotine films (14-day plus 3-day supply [68 films total]) to use over the next two weeks until their next study visit.

7.2.6.6 Participants will be asked to return all used (opened/empty) and unused (unopened) study product pouches at their next study visit.

7.2.6.7 Participants will be encouraged to remain abstinent from cigarettes.

7.2.6.8 Participants will be instructed to continue to maintain a daily diary of their nicotine film use. This diary will require that they record the time of day each film was taken. Participants will be instructed to only record cigarettes smoked on their diary in the event that they experience a slip.

7.2.6.9 Participants will be compensated for completing the study visit and procedures.

7.2.7 Cessation Phase – Phone Call #3 (Day 35 ± 3 days)

During this phone contact, daily cigarette/film diary information will be collected, adverse events or changes to concomitant medications will be documented, and participants will be asked to verbally answer the measures indicated in the Time and Events Table during the phone call. Participants' answers will be entered directly into REDCap by the researcher at the time of the call.

7.2.8 Cessation Phase – Visit 5 (Day 42 ± 3 days)

At this in-person visit, the following procedures will be conducted:

7.2.8.1 Adverse events will be documented, and any concomitant medication changes will be recorded.

7.2.8.2 The daily cigarette/film diary will be collected and recorded by the researcher. Use of other tobacco products in the past 7 days will also be assessed.

7.2.8.3 Participants will complete the measures and study procedures indicated in the Time & Events Table.

7.2.8.4 All nicotine pouches from the previous weeks (unopened, opened, or empty) will be collected by the researcher

7.2.8.5 Participants will be encouraged to remain abstinent from cigarettes.

7.2.8.6 Participants will be compensated for completing the study visit and procedures.

7.2.9 Study Visit Reminders

Phone calls and/or text messages will be used throughout the study to remind participants of their next visits (approximately 1-2 days prior) (SEE VISIT SCRIPT ATTACHMENT). Also, visit time/date confirmation and study center directions will be emailed/mailed to the participant prior to Visit 1 (SEE FIRST VISIT REMINDER ATTACHMENT).

7.3 Duration of Participation

Participants who complete the entire study will participate in the study for 7 weeks.

7.4 Test Article(s) (Study Drug(s) and/or Study Device(s))

7.4.1 Description

Nicotine orally dissolving films will be provided in doses of 0, 2, or 4 mg. The active pharmaceutical ingredient in these nicotine films is nicotine polacrilex (20%, USP). The film used in has a muco-adhesive property (i.e., it can adhere to the oral mucosa and allow the drug to be absorbed through oral mucosa). After placement in the oral cavity, the nicotine film dissolves over a 5 minute period. The unit-dose dosage is in the form of a 1 in x 1 in square and weighs

about 100 mg. Nicotine films are not available in the United States in a non-investigational setting. See table below for composition information.

Nicotine ODF Dosage		0 mg	2 mg	4 mg
Material Name	**Grade**	**Weight, g**	**Weight, g**	**Weight, g**
Sodium Bicarbonate	USP/EP	1.97	1.71	1.64
Propylene Glycol	USP/EP	23.66	20.55	19.68
Nicotine Polacrilex 20%	USP	0.00	17.81	37.72
Purified Water	USP	209.04	205.45	196.80
Ethanol anhydrous	USP	110.44	119.85	114.80
Polyox N10 (Polyethylene oxide)	NF	134.10	116.42	111.52
Saccharin	Food Grade	2.45	2.12	2.03
Cocoa Powder	Food Grade	1.77	1.71	1.97
L-Menthol	USP	9.98	8.66	8.30
Peppermint oil	USP	6.19	5.38	5.15
Methylparaben	NF	0.20	0.17	0.20
Propylparaben	NF	0.20	0.17	0.20
Total		500.00	500.00	500.00

7.4.2 Treatment Regimen

Nicotine films will be administered orally. They are used by placing a film on the tongue, closing the mouth, and pressing the tongue gently to the roof of the mouth. The film will dissolve in the mouth within 5 minutes. Three doses of nicotine film will be used in this study: 0, 2, and 4 mg.

Participants will be randomized to one of three possible treatment regimens:

1) **Random nicotine delivery** (a combination of four 0 mg and 4 mg films daily not to exceed three non-consecutive 4 mg films in one day and to maintain an average of 8mg of nicotine per day through 7 days for 6 weeks total)
    a) Possible weekly random delivery dosing scenarios to maintain an 8 mg/day average through 7 days:
        a. One 4mg day, five 8mg days, and one 12mg day in any order
        b. Two 4mg days, three 8mg days, and two 12mg days in any order

Possible Daily Sequences for Random Delivery		
4mg/day	**8mg/day**	**12mg/day**
4000	4400	4404
0400	4040	4044
0040	4004	
0004	0440	
	0404	
	0044	

2) **Steady state nicotine delivery** (2, 2, 2, 2 mg films daily for 6 weeks total)
3) **Placebo delivery** (0, 0, 0, 0 mg films daily for 6 weeks total)

Participants will be directed to take one film every 3-4 hours, in a specified order, for a total of four films consumed daily. In the event that participants miss taking a scheduled film, they will be instructed to skip the film if more than 8 hours has passed since they took their last film. They will be asked to indicate on their daily diary if a film was missed..

7.4.3 Method for Assigning Subject to Treatment Groups

Participants will be randomized to one of three dosing groups based on a predetermined random number sequence generated by the study statistician, Dr. Junjia (Jay) Zhu.

7.4.4 Subject Compliance Monitoring

Participants will be given a paper daily diary to complete on which they will record: 1) the number of cigarettes smoked each day, and 2) the date and time of each nicotine film taken. Participants will be given detailed instructions on how to complete the diary. Questions will be asked at each contact to review participants' logs and to verify their daily conventional cigarette and nicotine film use. Participants will also be asked to self-report their other tobacco use at each visit, including use of products such as electronic cigarettes, cigars, pipes, chew, snus, dip, hookah, and dissolvable tobacco. Exhaled carbon monoxide measurements will be collected throughout the study to verify smoking intensity.

Participants will be asked to return all of their used (empty/opened) and unused (unopened) nicotine film pouches to each study visit following Visit 2. At each of these visits, study staff will document the number of used and unused nicotine film pouches to verify participants' film use and compliance.

7.4.5 Blinding of the Test Article

Blinded packages of the nicotine films will be created for each participant by an unblinded pharmacy staff member. Both the participant and the researcher will be blinded to the assigned dosing regimen and to the doses of each film.

7.4.6 Receiving, Storage, Dispensing and Return

7.4.6.1 Receipt of Test Article

The nicotine films will be manufactured by Bionex Pharmaceuticals, LLC in its North Brunswick, NJ facility under cGMP conditions and shipped directly to Penn State Hershey Medical Center. The packaged test article has been tested to be stable at temperatures up to 30°C for 12 months, and therefore, will be shipped via courier under room temperature.

Each nicotine film will be individually packaged in a sealed, chemical- and moisture-resistant, multi-component (polyester/aluminized), laminated pouch.

7.4.6.2 Storage

The nicotine films will be stored in the Investigational Drug Services (IDS) Pharmacy at the Penn State Milton S. Hershey Medical Center in accordance with guidelines provided by the manufacturer.

7.4.6.3 Preparation and Dispensing

The nicotine films will arrive in individually sealed, peel-apart pouches. They will be blinded by pharmacy staff who will appropriately package kits containing each daily nicotine film dosing regimen to last the participant until the end of their next study visit window. The four individual films within each daily regimen's container will be numbered so that the films are taken in the appropriate sequential order each day. The blinded researchers will not be involved in the packing and labeling of the kits. All receiving, sorting, blinding of the study product will be done in IDS pharmacy space at Penn State.

7.4.6.4 Return or Destruction of the Test Article

Participants will be required to return all study products to the research center at each clinic visit, including any empty/opened pouches using provided containers/bags. Any remaining nicotine films will be destroyed according to Penn State IDS Pharmacy protocol at the conclusion of the study.

7.4.6.5 Prior and Concomitant Therapy

Concomitant medication use will be collected at baseline and regularly throughout the study to serve as covariates during analysis and to monitor participant health conditions. Participants currently using FDA approved cessation medications will be excluded. Should a participant start a medication during the randomized, double-blind phase of the study that would interfere with their ability to participate, they may be withdrawn from the study.

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

Participants will be enrolled in the study until a total of 45 are randomized. We anticipate that we will need to enroll up to 70 participants in order to randomize 45.

8.2 Sample size determination

Previous studies have shown the effects of NRT on cessation in sample sizes that are comparable to (e.g., Foulds, et al., 1992; Rose, et al., 1998; Rose, et al., 2006) the one proposed here (n=15 per treatment arm). Based upon such work, we are confident that we will have sufficient power to achieve the aim of the proposed research.

8.3 Statistical methods

Paired sample t-tests (or nonparametric Wilcoxon Rank-Sum tests) will be used to examine changes in the outcome measures (CPD, CO, subjective measures, BP, HR) from baseline.

9.0 Confidentiality, Privacy and Data Management

See the Research Data Plan Review Form.

9.1 Confidentiality

9.1.1 Identifiers associated with data and/or specimens

See the Research Data Plan Review Form.

9.1.1.1 Use of Codes, Master List

See the Research Data Plan Review Form.

9.1.2 Storage of Data and/or Specimens

See the Research Data Plan Review Form.

9.1.3 Access to Data and/or Specimens

See the Research Data Plan Review Form.

9.1.4 Transferring Data and/or Specimens

N/A

9.2 Subject Privacy

See the Research Data Plan Review Form.

10.0 Data and Safety Monitoring Plan

10.1 Periodic evaluation of data

The study coordinator and the PI will be responsible for the daily oversight of subject safety. Medical history will be reviewed by the study staff, and based on eligibility criteria, any questionable medical histories will be brought to the attention of the medical monitor for final inclusion determination prior to randomization. In a similar manner, contraindications for the treatment products and vital signs will be checked by study staff at each in person visit. The medical monitor will be available via phone for any consultations as necessary.

Subjects will be under medical supervision while in the study (i.e., by the medical monitor) and seen on an ongoing basis by our research staff who will document adverse events. The medical monitor will assess all adverse events and will be available for consultation over the phone for urgent matters. Otherwise, the PIs and/or the medical monitor will meet weekly with the study staff to review patient's progress and their experiences with the study products, including any adverse events.

10.2 Data that are reviewed

Data that will be reviewed include:

- Accrual and retention
- Medical history and concomitant medications
- Adverse events and serious adverse events
- Protocol deviations/violations

10.3 Method of collection of safety information

All data, including safety data, will be coded directly into REDCap electronic case report forms during study visits. Participant adverse events and serious adverse events will be assessed at each in-person study visit and each phone call visit but can be reported at any time during the study.

10.4 Frequency of data collection

Safety data, including adverse events and serious adverse events will be collected at each study contact.

10.5 Individuals reviewing the data

The study coordinator and the PI will be responsible for the daily oversight of subject safety. The PI and/or the medical monitor will meet weekly with the study staff to review patients' progress and their experiences with the study products, including any adverse events. For more urgent and/or serious adverse events, the medical monitor will be available for consultation by phone. The medical monitor will then make any needed medical recommendations and a determination regarding whether the participant is able to continue with the study.

10.6 Frequency of review of cumulative data

All of the data from the study (including adverse events) will be reviewed by the leadership group, including Dr. Sciamanna, on a regular basis to review patients' progress and their experiences with the study products.

10.7 Statistical tests

Statistical methods will be used to analyze the safety data to determine whether harms are occurring. Paired sample t-test (or nonparametric Wilcoxon Rank-Sum test) will be used to examine the changes in the outcome measures (CPD, CO, subjective measures, BP, HR) from the baseline.

10.8 Suspension of research

Due to the low risk of the intervention, it is unlikely that there will be a need to suspend the research. However, should the medical monitor, Dr. Sciamanna, identify any issues after reviewing the data, he can develop stopping rules for the trial, and his recommendations will be followed.

11.0 Risks

Potential risks for subjects are minimal. We have previously tested both single and repeat administration of each of the nicotine film doses which will be dispensed to subjects. We found that they were well-tolerated by subjects and produced nicotine levels in the blood that are less than subjects routinely receive from their cigarette smoking.[19] Subjects will have a review of their medical history prior to entry into the study. Subjects will be under medical supervision throughout their participation in the study, and adverse symptoms will be recorded by the research staff and monitored by the medical monitor and PIs. The major risks associated with the study are related to the use of nicotine (which is similar to the nicotine received from smoking) and nicotine withdrawal.

Additional potential risks include:

- **Nicotine film side effects:** Excess nicotine can cause mild symptoms such as nausea, dizziness, diarrhea, rapid heartbeat, heartburn, and hiccups. Occasionally these symptoms are more severe (e.g., vomiting) such as when an individual receives more nicotine than they are accustomed to. This, however, is unlikely to occur with the doses used in this study.
- **Nicotine withdrawal symptoms:** Ceasing conventional cigarette use may result in nicotine withdrawal symptoms (e.g., irritability, anxiety, restlessness, depressed mood, increased appetite, fatigue, difficulty concentrating). These symptoms will be monitored at each visit. Those receiving placebo films may experience more serious nicotine withdrawal symptoms.
- **Risk to fetus and breast fed infants:** Nicotine is known to be harmful to the developing human fetus, either from cigarettes or at the dose being used in this study. Women who are pregnant or are nursing a child may not participate in this research study. Women capable of becoming pregnant will be administered a pregnancy test prior to beginning the research. Participants must agree to take reasonable and necessary precautions against becoming pregnant during the period of the investigation.
- **Loss of confidentiality:** There is a risk of loss of confidentiality if information is obtained by someone other than the investigators. Precautions will be taken to prevent this including direct coding of data in REDCap.
- **Randomization:** Participants will be assigned to a treatment program by chance. The research intervention they receive may prove to have more side effects than the other research intervention(s).
- **Discomfort from questionnaires:** It is possible that some of the questions in the questionnaires may make participants uncomfortable. Participants will be instructed that they are free to skip any questions that make them uncomfortable.
- **Possible effects on the oral cavity:** Participants will be asked to report side effects including any mouth discomfort or irritation at each study contact. If indicated, a participant may discontinue study product use.
- **Incidental Finding:** None of the tests carried out in this study are intended to provide diagnoses for clinical purposes, but participants will be alerted to findings that should be discussed with a healthcare provider (such as high blood pressure).

12.0 Potential Benefits to Subjects and Others

12.1 Potential Benefits to Subjects

There is no guaranteed direct benefit to the individuals who participate in this study. However, those who participate and who are able to successfully quit smoking will have less exposure to tobacco-related toxicants as a result of their participation.

12.2 Potential Benefits to Others

Society as a whole will benefit from the research because it is expected to provide important information on the efficacy of nicotine film and random nicotine delivery as a potential method for smoking cessation.

13.0 Sharing Results with Subjects

This study is not designed to diagnose any disease or condition. However, if during the course of conducting clinical procedures (e.g., blood pressure), a participant is found to have a result outside of clinical norms, the result will be discussed with the participant at the visit where the result is identified. The participant will be given a letter indicating what procedure was done and will direct them to contact a medical provider for further evaluation. If a woman tests positive for pregnancy, the results will be shared with the participant, they will be withdrawn from the study, and they will be advised to follow up with their doctor for prenatal medical care.

14.0 Subject Stipend (Compensation) and/or Travel Reimbursements

Total compensation for the study is $140, which will be paid in both gift cards and checks. Actual payment will vary according to the number and type of contacts completed by each subject.

Participants will receive a $20 Walmart gift card upon completion of each in-person study visit. Those who complete all in-person study visits and who comply with the study product pouch return protocol (accurate returned pouches within a margin of 3 pouches at each visit following randomization) will receive a compliance incentive of $25. The compliance incentive will be paid in a check mailed to the participant's home upon completion of Visit 5.

Compensation for each completed phone call will be $5, for a potential total of $15, which will be paid in a cumulative check mailed to the participant's home only upon completion of Visit 5. If a participant did not complete any phone calls during the study, or if they did not complete Visit 5, they will not receive any of the potential $15 phone call compensation.

Time & Events Table								
Study Visit #	**1**	**2**	**Ph #1**	**3**	**Ph #2**	**4**	**Ph #3**	**5**
Study Week #	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Payment method	GC*	GC*		GC*		GC*		GC/CH*
Payments	$20	$20	Potential $5	$20	Potential $5	$20	Potential $5	$20 gift card + up to $15 for phone calls + $25 compliance incentive
Total	$20	$20		$20		$20		$60
*GC=Gift Card, CH=Check								

15.0 Economic Burden to Subjects

15.1 Costs

There will be no costs to the subjects for any of the procedures or tests associated with the study. Participants will be provided with the study products at no cost. Participants and/or their insurance companies will not be responsible for costs related to study procedures and tests.

15.2 Compensation for research-related injury

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

16.0 Resources Available

16.1 Facilities and locations

All participant visits will take place in the Penn State Hershey Clinical Research Center.

16.2 Feasibility of recruiting the required number of subjects

The smoking prevalence in South Central Pennsylvania is 19% of the adult population. Our recruitment strategy is designed to broadly disseminate information about the study to members of the community.

16.3 PI Time devoted to conducting the research

Drs. Grigson and Foulds have no clinical responsibilities and so the majority of their time is devoted to research, including this project. They are each funded at 5% time to this study.

16.4 Availability of medical or psychological resources

All of our participants will be seen by appropriately trained research staff. Any serious AEs or concerning test results will be passed on to participants along with a letter to their doctor. Any urgent health problem will require accompanying the participant to the ER, which is located in the same building as the clinical research center.

16.5 Process for informing Study Team

Regular team meetings will be conducted where study procedures, questions, and issues will be discussed and resolved.

17.0 Other Approvals

17.1 Other Approvals from External Entities

The FDA will require submission of an amendment to a previously approved IND (Investigational New Drug) application.

17.2 Internal PSU Committee Approvals

Check all that apply:

☐ Anatomic Pathology – Hershey only – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of HRP-902 - Human Tissue For Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ Animal Care and Use – All campuses – Human research involves animals and humans or the use of human tissues in animals

☐ Biosafety – All campuses – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Clinical Laboratories – Hershey only – Collection, processing and/or storage of extra tubes of body fluid specimens for research purposes by the Clinical Laboratories; and/or use of body fluids that had been collected for clinical purposes, but are no longer needed for clinical use. Upload a copy of HRP-901 - Human Body Fluids for Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☒ Clinical Research Center (CRC) Advisory Committee– All campuses – Research involves the use of CRC services in any way.

☐ Conflict of Interest Review – All campuses – Research has one or more of study team members indicated as having a financial interest.

☐ Radiation Safety – Hershey only – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload a copy of HRP-903 - Radiation Review Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☒ IND/IDE Audit – All campuses – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☐ Scientific Review – Hershey only – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Hershey Cancer Institute Scientific Review Committee is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website at: http://www.pennstatehershey.org/web/irb/home/resources/investigator

18.0 Multi-Site Research

18.1 Communication Plans
N/A

18.2 Data Submission and Security Plan
N/A

18.3 Subject Enrollment
N/A

18.4 Reporting of Adverse Events and New Information
N/A

18.5 Audit and Monitoring Plans
N/A

19.0 Adverse Event Reporting

19.1 Adverse Event Definitions

For drug studies, incorporate the following definitions into the below responses, as written:	
Adverse event	Any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related
Adverse reaction	Any adverse event caused by a drug
Suspected adverse reaction	Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than "adverse reaction". • *Reasonable possibility*. For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.

Serious adverse event or Serious suspected adverse reaction	Serious adverse event or Serious suspected adverse reaction: An adverse event or suspected adverse reaction that in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
Life-threatening adverse event or life-threatening suspected adverse reaction	An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator (i.e., the study site principal investigator) or Sponsor, its occurrence places the patient or research subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that had it occurred in a more severe form, might have caused death.
Unexpected adverse event or Unexpected suspected adverse reaction.	An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure, general investigational plan, clinical protocol, or elsewhere in the current IND application; or is not listed at the specificity or severity that has been previously observed and/or specified.

19.2 Recording of Adverse Events

Research subjects will be routinely questioned about adverse events at in-person study visits and during scheduled phone contacts.

All adverse events (serious or non-serious) and abnormal test findings observed or reported to study team believed to be associated with the study drug(s) or device(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy
    - NOTE**:** Simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.
- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study.
- The test finding is considered an adverse event by the investigator.

19.3 Causality and Severity Assessments

The medical monitor, Dr. Sciamanna, will promptly review documented adverse events and abnormal test findings on a weekly basis to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study drug(s) or device(s); and 3) if the adverse event meets the criteria for a serious adverse event. For more urgent and/or serious adverse events, the medical monitor will be available for consultation by phone. The medical monitor will then make any needed medical recommendations and a determination regarding whether the participant is able to continue with the study.

If the investigator's final determination of causality is "unknown and of questionable relationship to the study drug(s) or device(s)", the adverse event will be classified as associated with the use of the study drug(s) or device(s) for reporting purposes. If the investigator's final determination of causality is "unknown but not related to the study drug(s) or device(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

19.4 Reporting of Adverse Reactions and Unanticipated Problems to the FDA

19.4.1 Written IND/IDE Safety Reports

The Sponsor-Investigator will submit a written IND Safety Report (i.e., completed FDA Form 3500A) to the responsible new drug review division of the FDA for any observed or volunteered adverse event that is determined to be a serious and unexpected, suspected adverse reaction. Each IND Safety Report will be prominently labeled, "IND Safety Report", and a copy will be provided to all participating investigators (if applicable) and sub-investigators.

Written IND Safety Reports will be submitted to the FDA as soon as possible and, in no event, later than 15 calendar days following the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

For each written IND Safety Report, the Sponsor-Investigator will identify all previously submitted IND Safety Reports that addressed a similar suspected adverse reaction experience and will provide an analysis of the significance of newly reported, suspected adverse reaction in light of the previous, similar report(s) or any other relevant information.

Relevant follow-up information to an IND Safety Report will be submitted to the applicable review division of the FDA as soon as the information is available and will be identified as such (i.e., "Follow-up IND Safety Report").

If the results of the Sponsor-Investigator's follow-up investigation show that an adverse event that was initially determined to not require a written IND Safety Report does, in fact, meet the requirements for reporting; the Sponsor-Investigator will submit a written IND Safety Report as soon as possible, but in no event later than 15 calendar days, after the determination was made.

19.4.2 Telephoned IND Safety Reports – Fatal or Life-threatening Suspected Adverse Reactions

In addition to the subsequent submission of a written IND Safety Report (i.e., completed FDA Form 3500A), the Sponsor-Investigator will notify the responsible review division of the FDA by telephone or facsimile transmission of any unexpected, fatal or life-threatening suspected adverse reaction.

The telephone or facsimile transmission of applicable IND Safety Reports will be made as soon as possible but in no event later than 7 calendar days after the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

19.5 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

19.6 Unblinding Procedures

If an adverse event requires the subject to be unblinded, the unblinded study personnel (pharmacy staff) will be able to provide that information as needed. This will be reported appropriately along with the adverse event in accordance with the safety monitoring plan. Otherwise, participants will not be unblinded to their assigned study condition.

19.7 Stopping Rules

In the event of unexpected or serious adverse events that the study doctor, Dr. Sciamanna, believes are related to the study product, the IRB will be notified, and their recommendations will be followed.

20.0 Study Monitoring, Auditing and Inspecting

20.1 Study Monitoring Plan

20.1.1 Quality Assurance and Quality Control

The study will be monitored by the Clinical Trial Monitoring Team from the Department of Public Health Sciences at Penn State Hershey College of Medicine. The monitors will provide an independent review of the regulatory and subject records and the data collected to assure compliance with the protocol, GCP, and applicable federal regulations. The monitoring will occur at regular intervals after the enrollment of the first subject and the times will be predetermined by the monitoring plan developed by the Clinical Trial Monitoring Team.

Data will be collected from participants and coded directly by either using the REDCap survey tool (participant entered data) or through REDCap data entry forms (researcher entered data). The codes that link the name of the participant and the study ID will be kept confidential in REDCap. Any paper forms (i.e., consent) will be securely transported to the PI's data entry center. Any additional data that is generated will be stored electronically on the PHS server in password protected files.

Study data will be managed using REDCap (Research Electronic Data Capture). REDCap is a secure web application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation (e.g., for data types and range checks), audit trails, and a de-identified data export mechanism to common statistical packages (e.g., SPSS, SAS, Stata, R/S-Plus). The system was developed by a multi-institutional consortium which includes The Pennsylvania State University and was initiated at Vanderbilt University. The database is hosted at the Penn State Hershey Medical Center and College of Medicine data center, which will be used as a central location for data processing and management. REDCap data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team. This iterative development and testing process results in a well-planned data collection strategy for individual studies.

REDCap is HIPAA compliant. Data are stored on a secure server; data in REDCap are encrypted; access to the database requires authentication (a unique username and password); data are accessed based on the individual's role on the project; every interaction with the data is logged, creating an audit trail.

Random data entry checks will be implemented regularly to identify problems with data entry. Data quality tools included in REDCap will be utilized to identify incorrect data types, out of range data and outliers. In addition, electronic edit checks, and random internal quality and assurance checking will be performed manually. Data quality will be monitored by random inspection of the completed electronic forms by one of the research assistants and any

problems detected will be discussed with the PI. If necessary, re-training of researchers will be conducted.

The responsibility for data quality and study conduct lies with the PI.

20.1.2 Safety Monitoring

The principal investigator will confirm that all adverse events (AEs) are correctly entered into the AE case report forms by the coordinator; be available to answer any questions that the coordinators may have concerning AEs; and will notify the IRB, FDA, and/or sponsor of all applicable AEs as appropriate. All assessments of AEs will be made by a licensed medical professional who is an investigator on the research study.

The research coordinator will ensure that AEs are correctly entered into REDCap and complete the appropriate report form and logs; assist the PI to prepare reports and notify the IRB, FDA, and/or sponsor of all Unanticipated Problems/SAEs.

21.0 Future Undetermined Research: Data and Specimen Banking

21.1 Data and/or specimens being stored

N/A

21.2 Location of storage

N/A

21.3 Duration of storage

N/A

21.4 Access to data and/or specimens

N/A

21.5 Procedures to release data or specimens

N/A

21.6 Process for returning results

N/A

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